that smokers are not exposed to the dithiocarbamates. Only by-products of dithiocarbamates are present in mainstream tobacco smoke. The detectable levels of these by-products do not present a health risk to smokers (The meaning of the term "by-products" is discussed below in the section on Toxicological Evaluation of Dithiocarbamates). Therefore, persuasive scientific data does not support the enforcement of extremely low tolerance levels regarding dithiocarbamate residues (e.g., Thiram tolerance: 2 parts per million (ppm)) detectable in tobacco.

## Risk Perception and Regulation

Pesticide residues in food and drinking water have been the subject of publications in technical journals and in the lay press. One of the most prominent contributory factors to public awareness on the subject of pesticide residues is the tremendous advancement in analytical technology that has occurred in the last two decades. The technological developments in analytical methodology have provided the means to find small residues of pesticides in a variety of commodities where they were virtually undetectable only a few years ago. Man's understanding of the significance, if any, of such small amounts of pesticide residues is significantly less than his ability to detect these same levels.

The scope of regulation for limiting exposure to residues of pesticides used in agriculture should rely upon a determination of the degree to which consumers may be exposed to residues and the possible effects from such exposure. That determination must be based upon credible toxicological evidence. Unfortunately, the average individual's difficulty in understanding the difference between parts per million and parts per billion leads to a perception of heightened concern with the simple fact that detectable levels of residue are present in some product for human consumption. Such a reaction is not justified by sound scientific judgment. It is important, therefore, to place pesticides and their residue levels in the proper perspective in order for them to be properly understood. A chemical should not be perceived as a toxic risk simply because it has been used as a pesticide in agriculture. The mechanism of action that makes pesticides effective in controlling various pests and weeds does not necessarily translate to health concerns or adverse impact on the environment. The precise toxicology associated with a particular pesticide, taking into consideration the level of residue detectable in the product to which the consumer is exposed, should form the knowledge base upon which a reasoned judgment can be made about setting a tolerance on food commodities or tobacco.

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## Toxicological Evaluation of Dithiocarbamates

Dithiocarbamates constitute a chemical class of pesticides that are used by farmers primarily to control the growth of fungus on food commodities and tobacco. Among the class of dithiocarbamates are subclasses of chemicals that can be distinguished by differences in their molecular structure. Subclasses of the dithiocarbamates include ethylene bisdithiocarbamates (EBDCs, e.g., Maneb), propylene bisdithiocarbamates (PBDCs, e.g., Propineb) and dimethyl dithiocarbamates (e.g., Thiram). The only dithiocarbamate for which the Italian Ordinance has specified a tolerance level on tobacco is Thiram. The tolerance listed for Thiram is 2 ppm.(1) In contrast, the West German and Swiss governments have both determined that the recommended maximum level of residue on tobacco should apply to the entire class of dithiocarbamates (including Thiram) at a level of 50 ppm in the finished product.(2) The West German and Swiss regulations do not set tolerances for specific pesticides within the dithiocarbamate class. A twenty-five fold lower tolerance for dithiocarbamate residues on tobacco in Italy (e.g., Thiram), as compared to West Germany and Switzerland, is not supported by the toxicological evidence.

The class of dithiocarbamate pesticides are generally recognized as having a low order of acute (i.e., short term) oral or dermal toxicity as demonstrated by experimental studies in animals.(3) The large quantities of dithiocarbamate pesticides required to produce acute effects suggests a wide margin of safety regarding potential acute human exposures to residues. The potential chronic (i.e., long term) effects of dithiocarbamates have also been studied. The conclusion to be drawn from the carcinogenesis studies reported to date is that dithiocarbamates have not been shown to be carcinogens in either humans or animals.

The toxicology of specific dithiocarbamates has been thoroughly reviewed by the International Agency for Research on Cancer (IARC). IARC has classified the dithiocarbamate, Thiram, as a Group 3 chemical. This means that there is no human or animal evidence adequate to support a finding of carcinogenicity. Other examples of Group 3 chemicals among the class of dithiocarbamates are EBDCs known as Maneb and Zineb.(4)

Among the most important considerations in determining a particular tolerance level is the potential for exposure to the consumer through the product to be consumed. Tolerances specified for food commodities can be assigned to the raw product in most cases because of the lack of any significant change in the form or condition of the product from the field to the consumers dinner table. In contrast, tobacco undergoes substantial transformation

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# DITHIOCARBAMATE PESTICIDES USED ON TOBACCO

## A TECHNICAL OVERVIEW

### Introduction

During the last several years there has been increased attention in many countries regarding the use of pesticides in the production of agricultural products. The term "pesticide" includes chemicals used to control the spread of insects (insecticide), weeds (herbicide), fungi (fungicide) rodents (rodenticide) and other organisms that can cause substantial production losses in agriculture as well as present a nuisance, in some cases an actual health hazard, in homes and communities throughout the world. Pesticides are now an important part of worldwide agricultural success. The development of progressive scientific farming spawned research and educational efforts which have lead to an extensive use of pesticides in all areas of agricultural production. Without the use of these pesticides, agricultural operations would not be economically feasible.

As with any other crop, including all food products, farmers use pesticides on growing tobacco in order to attain production levels that are economically feasible and competitive in the world market. The ultimate goal, to provide the consumer with a quality product, cannot be achieved without maintaining the integrity of the tobacco plant through treatment with pesticides. Indeed, tobacco, as well as many other crops, could not profitably be produced without the assistance of pesticides. Insecticides, herbicides and fungicides are applied by farmers to soil prior to planting, plant beds, and directly to growing plants. Among the pesticides used by tobacco farmers is the chemical class known technically as "dithiocarbamates." The dithiocarbamates are used mostly as fungicides to protect against damage to the tobacco plant that is likely to occur when it is grown in a wet climate favorable to fungal infestation. The necessary use of these fungicides sometimes results in very small residual amounts of the chemical being detectable on the tobacco used in manufacturing cigarettes.

The following technical discussion is intended to address the scientific issues relevant to the Italian Health Ministry's consideration of pesticide regulation on tobacco. In particular, this paper is focused on the need for the Ministry to reevaluate its approach to regulation of the dithiocarbamates. An alternative proposal to the existing regulations, set out in the Italian Ordinance, is suggested based upon the scientific data and the necessities of tobacco agricultural practices. A review of the toxicological evidence indicates that residues of dithiocarbamates which may be present in the finished cigarette do not present a health hazard to cigarette smokers. The data strongly suggests

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from the raw leaf at harvest to the manufactured cigarette because of the various curing and processing procedures that are necessary to achieve a finished product acceptable to the consumer. As a result of this transformation of the tobacco, any residues present on the raw leaf will differ substantially from the levels detectable in the manufactured cigarette. Therefore, any tolerance that applies to pesticide residue on tobacco should apply only to the finished product. Such an approach would represent the only realistic method to assess potential exposure to the consumer.

Another key consideration for determining a tolerance level, which is also important in the toxicological evaluation of pesticide residues on tobacco, is the extent to which the pesticide transfers into the mainstream smoke to which the smoker is actually exposed. This factor is of particular importance when dithiocarbamates are studied as a residue in tobacco. In 1962, Barkemeyer, et al., published an article in Beitrage Zur Tabakforschung which examined the effect of combustion on dithiocarbamate residues under standardized smoking conditions. The article reported that dithiocarbamate (in particular, EBDCs) residues detectable in the cigarette tobacco were not found in the mainstream smoke.(5) The authors demonstrated that the EBDC residues in cigarette tobacco were converted, predominantly, to small amounts of carbon disulfide and hydrogen sulfide in the mainstream tobacco smoke. These combustion by-products have not been demonstrated to be of toxicological concern at the levels they may be present in mainstream tobacco smoke. In addition, these same by-products (carbon disulfide and hydrogen sulfide) can form from precursors (e.g., amino acids and proteins) naturally present in tobacco. These findings reported by Barkemeyer are corroborated by Lorenz, et al., who conducted experiments using a radiolabeled dithiocarbamate pesticide, Maneb. These studies were designed to evaluate the physical and chemical behavior of the dithiocarbamate residues on cigarettes under standardized smoking conditions. Lorenz reported that no unchanged dithiocarbamates were detectable in the mainstream smoke. In particular the studies demonstrated that the transfer rate (yield) of potential dithiocarbamate combustion by-products into mainstream smoke was approximately 12.8 percent.(6,7) A Finnish investigator, Autio, attempted to find a specific chemical in cigarette smoke condensate that has been associated with the breakdown of dithiocarbamates (in particular, EBDCs), known as ethylene thiourea (ETU). Autio reported the detection of trace amounts of ETU.(8) Inherent limitations in the analytical methods used by Autio raise serious questions regarding the accuracy of the trace levels reported and the extent to which any ETU actually detected could be attributed to the presence of EBDC on the tobacco.

One study has reported findings that are not consistent with the Barkemeyer, Lorenz, or Autio studies. Mestres, et al.,

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reported that dithiocarbamate by-products (in particular, ETU) were present in mainstream tobacco smoke at a level that represented greater than 50% breakdown yield from known EBDC residue on the tobacco. (9) The Mestres study has serious methodological flaws and its findings are not consistent with the known chemical characteristics of EBDCs or ETU. Thiram (a non-EBDC dithiocarbamate) is not known to result in ETU formation.

In summary, residues of dithiocarbamate pesticides in the finished tobacco product do not result in any detectable transfer of the parent compounds into mainstream smoke. Further, the trace levels of by-products of dithiocarbamates that may be detectable in mainstream smoke have not been demonstrated to be a toxicological concern. Thus, a scientific evaluation of the dithiocarbamate pesticides does not justify a highly restrictive tolerance level in Italy.

## Residue Regulatory Issues Unique to Tobacco

As discussed above, raw leaf tobacco is substantially transformed through the extensive post-harvest procedures that are required before it is incorporated into a quality finished tobacco product acceptable to the consumer. Raw tobacco may be stored as long as 3 to 4 years before it is cut, blended and processed into the finished product. The nature and extent of transformation that occurs in tobacco is not apparent in most agricultural food commodities before they are made available for consumption. This basic difference between food products and tobacco products forms the foundation for suggesting that tolerance levels for pesticides on tobacco should apply to the finished product. Such an approach differs from the apparent application of tolerances to the raw agricultural commodity with respect to food products and tobacco in the Italian Ordinance.

In the United States the use of pesticides on all agricultural products, including tobacco, is approved and otherwise regulated by the U.S. government, principally the Environmental Protection Agency (EPA). Residue tolerance levels have been established for food and animal feed products. Tobacco is not considered to be "food" in the U.S. and maximum residue levels on tobacco exist only for certain pesticides prohibited for use on tobacco. Thus, the distinction to be made between regulation of residues in food vs. tobacco is reflected in the U.S. scheme of pesticide regulation.

West Germany's regulation of pesticides recognizes the importance of applying tobacco tolerances to the finished product in contrast to the raw commodity norm that generally applies to

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foods. The current West German regulations have been in place since 1978 and represent the most comprehensive set of recommended tolerance levels on tobacco in the European community. Many of West Germany's neighbors use the same regulations to govern pesticide tolerance levels in their own country. The West German regulations specify maximum permitted levels on tobacco for residues of 13 pesticides. The use of 71 other plant protection chemicals is also allowed if good agricultural practices are followed. The residues for these 71 chemicals should not exceed a recommended maximum amount. These residue levels are applicable to tobacco in the finished product. For example, the 50 ppm recommended maximum residue level for dithiocarbamates is applied to tobacco as it would be found in a manufactured cigarette. This represents the approach that is most relevant to determining the potential exposure of the smoker to any pesticide residue which may be detectable in tobacco.

In contrast, under the Italian Ordinance, food products and tobacco are treated alike and appear in the same norm. This approach does not consider the obvious differences in processing and consumption between food and tobacco. In addition, it is inconsistent with the regulation of pesticide residues in other countries and it is not supported by the available scientific information.

## Conclusion

The regulation of pesticide residues on tobacco in Italy should relate to the levels detectable in the finished products that are made available for distribution to the consumer. Application of any residue tolerances to the finished product would address the concerns of the Italian Health Ministry regarding potential exposures of tobacco smokers to pesticides.

The chemical class of dithiocarbamates present a toxicological profile that does not support enforcement of highly restrictive tolerances exemplified by the 2 ppm level specified for Thiram in the Italian Ordinance. No residues of dithiocarbamate pesticides have been shown to transfer into mainstream smoke. The trace levels of dithiocarbamate by-products that may be detectable in tobacco smoke have not been demonstrated to be a toxicological concern. The Italian Health Ministry should give serious consideration to a regulatory approach that is consistent with that adopted by other countries on finished product tobacco.

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